Advice on assistance and protection from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons : Part 2. On preventing and treating health effects from acute, prolonged, and repeated nerve agent exposure, and the identification of medical countermeasures able to reduce or eliminate the longer term health effects of nerve agents

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Running head: Treating the long-term effects of nerve agents

Abstract

The Scientific Advisory Board (SAB) of the Organisation for the Prohibition of Chemical Weapons (OPCW) has provided advice in relation to the Chemical Weapons Convention on assistance and protection. We present the SAB's response to a request from the OPCW Director-General in 2014 for information on the best practices for preventing and treating the health effects from acute, prolonged, and repeated organophosphorus nerve agent (NA) exposure. The report summarises pre- and post-exposure treatments, and developments in decontaminants and adsorbing materials, that at the time of the advice, were available for NAs. The updated information provided could assist medics and emergency responders

unfamiliar with treatment and decontamination options related to exposure to NAs. The SAB recommended that developments in research on medical countermeasures and decontaminants for NAs should be monitored by the OPCW, and used in assistance and protection training courses and workshops organised through its capacity building programmes.

Keywords: Bioscavenger; Chemical Warfare Agent; Chemical Weapons Convention; Decontaminant; Nerve Agent; Organisation for the Prohibition of Chemical Weapons.

1. Introduction

Upon joining the Chemical Weapons Convention (hereinafter "the Convention"), member nations ("States Parties") commit to never develop, produce, otherwise acquire, stockpile, retain or use chemical weapons (OPCW, 1997). The Convention permits the development of national programmes for protection against chemical weapons, supported by the Organisation for the Prohibition of Chemical Weapons (OPCW), the implementing body of the Convention, headquartered in The Hague, the Netherlands. The States Parties to the Convention are required to provide assistance and protection to fellow Member States threatened by or attacked with chemical weapons, and a State Party may request this assistance and protection through the OPCW. Resources from a Voluntary Fund for Assistance, as well as individual offers of equipment and trained personnel, are available and a network of protection experts consult regularly on means to improve the capabilities of States Parties to respond to chemical incidents. Such assistance may include, but is not limited to, items such as detection and alarm systems, protective equipment, decontamination equipment, medical antidotes and treatments (OPCW, 2016a) and advice on protective measures (OPCW, 2017a, 2018a). The OPCW also has a rapid response and assistance capability that States Parties can call upon if required (OPCW, 2016b).

The OPCW has a Scientific Advisory Board (SAB) comprised of 25 members appointed from all regions of the world that advises the OPCW Director-General on developments in

scientific and technological fields relevant to the Convention (OPCW, 2018b). This includes the provision of advice on technical matters related to international cooperation. At its Twentieth Session in June 2013, the Director-General requested the SAB to give advice on assistance and protection against chemical weapons (OPCW, 2013). The SAB provided the Director-General with a response (OPCW 2014a) that recommended pretreatments and post-exposure treatments that are available for countering the toxic effects of nerve agent (NA) chemical warfare agents (CWAs). This advice forms the substance of Part 1 of this series of papers (Timperley et al., 2018a) and that text should be consulted in parallel.

To capture insight on the long-term damage caused by CWAs, and emerging medical countermeasures to them, an additional question was introduced by the Director-General to the SAB at its Twenty-First Session in June 2014 (OPCW, 2014b). Then, in light of victims of chemical weapons undergoing medical care due to use of the organophosphorus nerve agent (NA) sarin in the Syrian Arab Republic (Fischer et al., 2016; Timperley et al., 2018b), there was a compelling need to understand better what could be done to mitigate the long term effects of CWAs, especially NAs, in humans. Such information would also be a valuable addition to the International Support Network for Victims of Chemical Weapons that was established by the OPCW in 2011 (OPCW, 2011, 2012). The SAB was thus requested to identify any emerging medical countermeasures which could reduce or eliminate the long-term health effects arising from acute, prolonged, and repeated exposure to NAs.

This paper, the second of a series on medical countermeasures and treatment, contains the SAB's response provided to the Director-General and States Parties on 10 June 2015 (OPCW, 2015a). It is augmented by the addition of extra background information and references. Adjuncts to traditional medical countermeasure approaches to NA poisoning, including neuroprotective agents and bioscavengers, along with methods of decontamination are described. The material in this paper assumes familiarity with the previous paper (Part 1: Timperley et al., 2018a) which described the medical care and treatment of injuries from blister agents and NAs along with experimental and clinical findings.

Deducing the mechanisms underlying toxic syndromes associated with both classes of CWAs is an enduring task (Aas, 2003; Balali-Mood and Abdollahi, 2014; Costanzi et al., 2018; Myhrer and Aas, 2014; Myhrer et al., 2006, 2013, 2015; Timperley and Tattersall, 2015). This is especially true for organophosphorus (OP) compounds which can cause long-term neurological damage (Abdollahi and Karimi-Mojaheri, 2012; Akhgari et al., 2003; Balali-

Mood and Balali-Mood, 2008; Brown and Brix, 1998; Karalleide et al., 2006; Hung et al., 2015; Somani and Husain, 2000; Tattersall, 2018).

1.1. Legal disclaimer

This report contains information, guidelines, diagrams and other materials addressed to medical practitioners who are engaged in the treatment of casualties of chemical weapons. It is made available to the public for information purposes, but is not intended to be used by the public. All decisions regarding patient care must be made with a healthcare provider and consider the unique characteristics of each patient. The views and opinions expressed in this report and in the suggested reading materials are those of the authors and do not reflect the views of the OPCW. These materials are cited as a service to readers and do not imply endorsement by the OPCW or the individuals involved in the development of this report. The OPCW and any of the individuals involved in the development of this report are not responsible for the content of third party websites. The information contained herein is accurate to the best of the authors' knowledge. However, neither the OPCW nor the authors shall be liable under any circumstances for the correctness, accuracy or comprehensiveness of such information, or for the consequences of its use.

2. Late effects of organophosphorus compounds

Poisoning from OP compounds produces three principal clinical syndromes: (a) acute cholinergic syndrome intermediate syndrome (IMS); and (c) OP-induced neuropathy (OPIDN) (Timperley and Tattersall, 2015; Lotti and Moretto, 2005). The acute cholinergic crisis develops within minutes to several hours after exposure, depending on the OP compound and the route of poisoning (Timperley et al., 2018a). Death can take place in a short time if life-threatening conditions, such as respiratory failure, are not treated rapidly and appropriately. OPIDN occurs 2-3 weeks following acute exposure to certain OP insecticides (Timperley and Tattersall, 2015). The clinical picture is usually a numbness and weakness of the lower extremities, followed by progressively ascending weakness of limb muscles. The IMS (Senanayake and Karalleide, 1987) occurs in the interval between the end of the acute cholinergic crisis and the onset of OPIDN. It is indicated by weakness and fatigue of skeletal muscles with fasciculation, leading to paralysis of the respiratory muscles, and is considered a major contributing factor to OP-related morbidity and mortality.

Neurotoxicity is the main late effect of OP compounds that can occur after an acute exposure (Mostafalou and Abdollahi, 2018). The IMS and OPIDN usually occur 24-96 hours and 1 to 3 weeks after an acute exposure to OP compounds, respectively. The neuropathy can progress in months or years after acute and chronic exposure. Persistent inhibition of AChE is initially responsible for muscle weakness, but is not the only factor involved in the occurrence of the IMS or neuropathy. Therefore, the AChE assay cannot be a sensible index for determining nerve and muscle function impairment. IMS usually occurs after an acute cholinergic crisis, while a neuropathy may occur after acute and chronic exposures (Karami-Mohajeri et al., 2014). Studies of acute OP poisoning in experimental animals have revealed that muscle necrosis is much more severe in the diaphragm compared to other skeletal muscles (Abdollahi and Karami-Mohajeri, 2012).

Several mechanisms are involved in the etiology of the IMS. They include inhibition of acetylcholinesterase (AChE), muscle necrosis, down-regulation or desensitization of postsynaptic acetylcholine (ACh) receptors, a failure of presynaptic ACh release, and oxidative stress-associated myopathy. In this regard, other factors such as lipophilicity, duration of the existence of the main compound or its metabolites in the body, the potency of the compound in inhibiting the AChE, severity of influence on repetitive nerve stimulation, and type and frequency of the muscle lesions, also matter in the prognosis of the IMS. Plasma AChE of less than 200 units and a reduction of 30 Hz repetitive nerve stimulation response can help diagnose the IMS (Abdollahi and Karami-Mohajeri, 2012).

It is well known that respiratory muscle dysfunction is one of the major causes of death in acute OP poisoning through muscular paralysis (Seeger et al., 2012). Thus, hypothetically, electromyography can help diagnosis but its value is uncertain. Electromyographical changes during the IMS include electrical stimulus-induced repetitive and decremental responses, tetanic fade, and a decrement-increment response at higher frequencies of repetitive nerve stimulation. Normal nerve conduction velocities and distal latency may be noted. The recurrent stimulation of nicotinic receptors through presynaptic feedback or desensitization of postsynaptic receptors may reduce the release of ACh (Karami-Mohajeri et al., 2014).

Some of the toxic effect of OP compounds arises from mitochondrial oxidative phosphorylation dysfunction mediated through the inactivity of complexes I, II, III, IV and V and mitochondrial membrane damage. Reduced synthesis of adenosine triphosphate (ATP) or induction of its hydrolysis can cause the cellular energy deficit. Also, OP compounds can

damage mitochondrial antioxidant defences by overproducing reactive oxygen species, activating caspases and triggering cell death. This mitochondrial dysfunction is repaired by the use of antioxidants such as vitamins E and C, electron donors, and through increasing the cytosolic ATP level (Karami-Mohajeri et al., 2013). However, to elucidate many aspects of mitochondrial toxicity of OP chemicals, further studies are required.

Some therapies are underway for the management of chronic neuropathies, especially ones related to the oxidative stress that is also evident in OP-induced chronic neuropathy. These therapies include taurine, acetyl-L-carnitine, alpha-lipoic acid, protein kinase C inhibitor (ruboxistaurin), aldose reductase inhibitors (fidarestat, epalrestat, ranirestat), advanced glycation end-product inhibitors (benfotiamine, aspirin, aminoguanidine), the hexosamine pathway inhibitor (benfotiamine), and inhibitors of polyADP-ribose, polymerase (nicotinamide), and angiotensin-converting enzyme inhibitor (trandolapril) (Hosseini and Abdollahi, 2013).

3. Adjunct agents and new trends in the treatment of nerve agent poisoning

We now describe a range of drugs that have been tested experimentally for neuroprotective purposes in experimental animal models involving prior administration of NAs, sometimes in combination with traditional medical countermeasure drugs (e.g. atropine and an oxime). For further details of such traditional drug approaches to ameliorating poisoning by OP pesticides and NAs (structures of NAs were derived from pesticide research originally; Timperley, 2000), see Part 1 of this series of papers. The chemical structures of some of the neuroprotective drugs now discussed appear in Figure 1. Further details on neuropathology and neuroprotective drugs in relation to the treatment of toxicity arising from exposure to NAs are available in recently published reviews (Moshiri et al., 2012; Tattersall, 2009; Timperley and Tattersall, 2015).

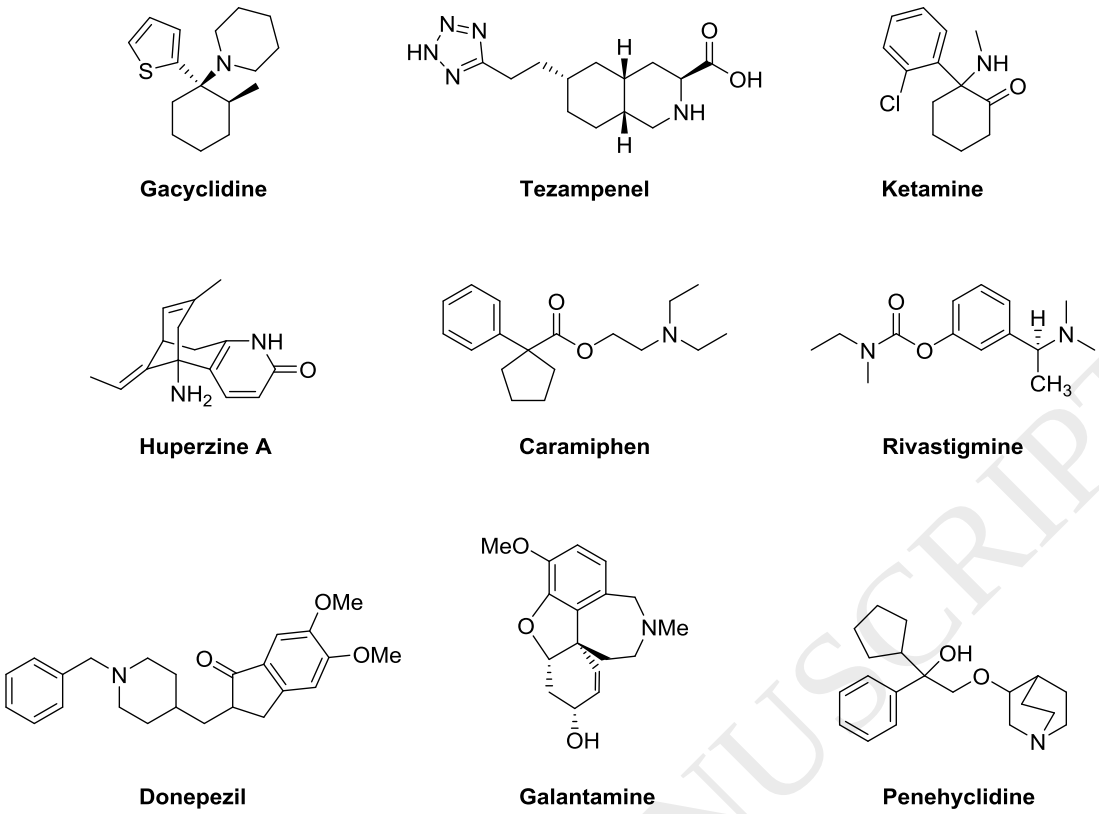

Figure 1. Structures of some of the neuroprotective agents tested to alleviate NA poisoning.

3.1. Neuroprotective agents

3.1.1. Gacyclidine

Gacyclidine (GK-11) was studied in experimental and clinical trials for different neuroprotective indications (Bhagat et al., 2005; Hirbec et al., 2001). It is a new phencyclidine derivative that binds to *N*-methyl-D-aspartate (NMDA) receptors, and also to non-NMDA binding sites located in the cerebellum and on the dendritic tree of Purkinje cells. Gacyclidine prevents glutamate-induced neuronal death, reduces the size of lesions after traumatic brain injury (Smith et al., 2000), and enhances the neuroprotective activity of atropine, pralidoxime and diazepam in soman poisoning. The clinical findings and electroencephalography (EEG) recordings revealed that convulsions could be prevented in soman experiments using primates (Lallement et al., 1999a, 1999b). Optimal effects were achieved within 30 min of poisoning. Gacyclidine was useful in inhibiting neuropathological changes occurring 3 weeks after a soman challenge (Balali-Mood and Saber, 2012).

Unfortunately, gacyclidine production was stopped several years ago, and the drug is no longer available for experimental studies in animals or for clinical trials in humans due to patent rights. Ketamine, a weaker NMDA antagonist, with a large clinical use worldwide might be considered instead for the treatment of NA-induced refractory status epilepticus (Dhote et al., 2012) (see Section 3.1.3. for more information on ketamine as a possible neuroprotectant).

3.1.2. Tezampanel

Tezampanel (LY293558) is an anti-glutamatergic agent with a specific affinity for kainate sub-type receptors (Ornstein et al., 1993). In experimental animals it reduced the length of status epilepticus and neuropathy induced by soman (Figueiredo et al., 2011b). The best results were achieved when it was administered within 1 h after exposure. Tezampanel can prevent brain pathology and is applicable to the paediatric population (Miller et al., 2015).

3.1.3. Ketamine

Ketamine is a cyclohexanone derivative that blocks NMDA receptors non-competitively. A study with soman-poisoned guinea pigs showed that ketamine effectively stopped the seizures and reduced related brain damage when administered 1 h after exposure (Dorandeu et al., 2005, 2013). Co-administration of benzodiazepines provided a synergistic effect, and when used with atropine, an additional neuroprotective effect (suppression of neutrophil granulocyte infiltration and partial suppression of glial activity) (Dhote et al., 2012). The additional benefit of ketamine and atropine was explained by NMDA antagonism, possible reduction of glutamate release, and the anticholinergic effect of atropine. Similar benefits have been observed in mice and rats. However, ketamine is not an approved drug for the treatment of NA victims.

3.1.4. Huperzine A

Huperzine A is an alkaloid purified from Chinese club moss that is used to treat Alzheimer's disease and myasthenia gravis (Zangara, 2003; Zhi et al., 1995). It inhibits AChE reversibly, similar to donepezil, rivastigmine or galantamine (Aracava, 2009). A beneficial effect of reducing the severity of seizures and prevention of status epilepticus after NA poisoning, by

blocking the NMDA receptors (Coleman et al., 2008; Zhang et al., 2001), has been shown in animal experiments (Aracava et al., 2009; Garcia et al., 2009; Grunwald et al., 1994).

3.1.5. Caramiphen

Caramiphen is an antimuscarinic drug with antiglutamergic and gabaergic properties. Its therapeutic efficacy against OP-poisoning as a prophylactic and post-exposure treatment has been confirmed in several experimental studies (Figueiredo, 2011a; Raveh et al., 2002, 2014).

3.1.6. Galantamine

Galantamine (GAL) inhibits AChE and potentiates ACh-induced currents in brain neurons (Aracava, 2009). It also potentiates the activity of NMDA receptors, an action which is partially responsible for the improvement of neurocognitive function in patients with Alzheimer's disease. In contrast to pyridostigmine and physostigmine that also inhibit BuChE, it should help preserve the scavenging capacity of plasma BuChE for OP compounds. It crosses the blood-brain barrier, protecting the brain AChE from OP-induced irreversible inhibition. Magnetic resonance imaging revealed that galantamine, administered 30 min prior to exposure of guinea pigs to a lethal dose of soman, prevented brain damage (Gullapalli et al., 2010). Galantamine is absorbed rapidly with absolute oral bioavailability between 80% and 100%. It has a half-life of 7 h. Peak inhibition of AChE was achieved ~1 h after a single oral dose of 8 mg in some healthy volunteers. In one study, performed in guinea pigs challenged with 16.8 μg/kg VX (2 × LD_{50}), GAL hydrobromide antagonised VX-induced lethality, impairment of muscle tension, and EEG changes (Hilmas et al., 2009). Optimal clinical effect was found with 10 mg/kg GAL. It did not alter seizure onset induced by VX, but significantly decreased seizure duration when administered as a post-exposure treatment against 2 × LD_{50} VX.

3.1.7. Penehyclidine hydrochloride

The anticholinergic agent penehyclidine hydrochloride (Niu et al., 1990) has been used clinically for treating poisoning by organophosphorus pesticides. Previous studies confirmed its ability to cross the blood-brain barrier and antagonise muscarinic and nicotinic receptors in the brain (Li et al., 2003). Penehyclidine hydrochloride was able to treat ongoing seizures

and had a better neuroprotective effect if administered soon after seizure onset in soman poisoning in experimental animals (Wang et al. 2005).

3.2. Treatments involving inorganic salts

Treatments involving administration of sodium hydrogen carbonate or magnesium sulfate have been investigated for amelioration of OP-poisoning and are discussed next.

3.2.1. Sodium hydrogen carbonate and blood alkalinisation

Sodium hydrogen carbonate has been explored as a means of increasing blood alkalinity to accelerate the hydrolysis of OP molecules *in vivo* (Antonijvic et al., 2002; Nurulain, 2012). The effects of high doses of sodium hydrogen carbonate (5 milliequivalent/kg (mEq/kg) in 1 h, followed by 5 mEq/kg/day) were assessed (Vučinić et al., 2009). Adjustment of the dose according to the arterial blood gas analysis was necessary. Increasing one unit of pH was accompanied by a 10-fold increase in OP hydrolysis, and alkalinisation products of NAs such as those from soman were less toxic. Hence, blood alkalinisation may be beneficial in NA poisoning. The proposed mechanism involves better control of cardiotoxicity, increased bio-availability of oximes (Buckley et al., 2011), increased atropine activity, and/or a direct effect of sodium hydrogen carbonate on neuromuscular function. The administration of sodium hydrogen carbonate is not yet established as a standard procedure.

3.2.2. Magnesium sulfate

The mechanism of action of magnesium sulfate is inhibition of ACh release through blocking calcium channels in the central nervous system (CNS) and at peripheral sympathetic and parasympathetic synapses (Fuchs-Buder, 1996). Its efficacy in the treatment of acute OP poisoning has been evaluated in several studies: these have shown decreased mortality and reduced overstimulation of the CNS due to NMDA receptor activation (Basher and Rahman, 2013; Eddleston et al., 2008). Doses of 4-16 g of magnesium sulfate were assessed and no side effects were observed (Pajoumand, 2004). However, there is still insufficient evidence to recommend the routine use of magnesium sulfate for treating NA casualties.

3.3. Treatments involving antioxidants

Besides the inhibition of AChE, the mechanism of OP compound poisoning possibly includes induction of oxidative stress and generation of free oxygen radicals (Balali-Mood et al., 2006, 2012; Moshiri et al., 2012), indicated by the increased activity of catalase, superoxide dismutase, glutathione peroxidase, and the concentration of malondialdehyde in red blood cells and the liver as a biomarker of oxidative stress (Hosseini and Abdollahi, 2013). Chronic toxicity studies have revealed an increased level of oxidative stress biomarkers as well as increased DNA damage. A beneficial effect of vitamin E and *N*-acetyl-L-cysteine has been demonstrated in experimental studies. However, there is still insufficient evidence to recommend the routine use of drugs that ameliorate oxidative stress in NA casualties.

3.4. Treatments involving protective bioscavengers

New treatments to counter NA poisoning should provide reduced lethality, reverse the toxicity following exposure, and help eliminate the necessity for further medical intervention. The need to start treatment within 1 min after exposure to be effective against poisoning by all OP compounds has prompted the development of pretreatment therapy, such as bioscavengers (Mann et al., 2018; Moshiri et al., 2012; Mumford et al., 2011, 2013; Rice et al., 2016, Masson and Nachon, 2017). Bioscavengers are enzymes, antibodies, or other chemicals that sequester and neutralise toxic OP compounds before they reach their biological targets (Figure 2).

If enzymes are to be used as therapeutic agents, they should:

(a) have a large spectrum of activity versus different NAs and a rapid activity;

(b) have a suitable retention time in circulation (ideally 11-15 days);

(c) be available in sufficient concentration to be effective;

(d) have no immunogenic properties; and

(e) be available at a reasonable cost.

The classes of available bioscavengers available are:

(a) Stoichiometric bioscavengers - cholinesterases (ChEs), especially butyrylcholinesterase (BuChE) (Boyko et al., 2019; Nicolet et al., 2003), and carboxylesterases (CaEs) (Jokanović et al., 1996; Fleming et al., 2007) which react stoichiometrically with OP compounds.

(b) "Pseudocatalytic bioscavengers" that combine BuChE or AChE, that have scavenging properties and bind NAs, and an efficient oxime reactivator, establish cycles of enzyme inhibition and reactivation, enabling the degradation of the NAs (Kovarik et al., 2015; Maček Hrvat et al., 2016; Radić et al., 2013).

(c) Catalytic bioscavengers (OP hydrolase, OP anhydrase, and paraoxonase (PON) enzymes (Ben-David et al., 2012)) that trap and degrade neurotoxic OP compounds rendering them non-toxic (Blum et al., 2008; Briseño-Roa et al., 2006, 2011a, 2011b; Masson et al., 2016; Timperley et al., 2006; Worek et al., 2016). Also, cyclodextrins modified with oxime functionality are able to encapsulate certain NAs in aqueous media and catalyse their hydrolysis to low toxicity products (Zengerle et al., 2011) including the NA acids (Barucki et al., 2003; Timperley et al., 2001).

3.4.1. Stoichiometric bioscavengers

When used as a pretreatment in mice, fetal bovine serum AChE provided complete protection against VX, lower protection against soman, and in conjunction with atropine and 2-PAM in a post-exposure treatment, protection against VX and soman (Wolfe et al., 1987). In one study on rhesus monkeys, equine serum BuChE protected against 2 × LD_{50} of soman, and 4 × LD_{50} when atropine was used in the post-exposure treatment (Maxwell et al., 1992).

Plasma-derived human BuChE (pHuBuChE) scavenging properties against different NAs were evaluated in mice, rats (Brandeis, 1993), and rhesus monkeys, and showed a linear correlation between the concentration of pHuBuChE and the level of protection against soman, sarin and VX. Prophylactic pHuBuChE has several advantages for human use such as: rapid reaction with a broad spectrum of OP compounds, a good retention time in circulation (Chilukuri et al., 2005), and no immunogenic activity. After extrapolation of data from animal experiments to humans, a dose of 200 mg of pHuBuChE has been estimated as a prophylaxis for humans in the case of exposure to 2 to 5 × LD_{50} of soman. For mass production of pHuBuChE two methods are currently available: purification of the enzyme from human plasma (Cohn Fraction IV) developed by Baxter Health Care Corporation or the

use of recombinant human enzyme produced in the milk of transgenic goats ('Protexia', developed by Nexia) (Cerasoli et al., 2005). Recently an investigation focused on identifying a safer source of HuBuChE. Possible sources of recombinant HuBuChE (rHuBuChE) are transgenic plants, transgenic animals, transfected larvae, adenovirus or algae, and rHuBuChE can also be derived in cell lines.

CaE is synthesised in the liver and afterwards is present in the circulation in different concentrations in mammals. However, humans do not express CaE in their circulation and further studies are needed before considering CaE for use as a bioscavenger (Duysen et al., 2011).

Fresh frozen plasma (FFP) is a blood fraction prepared by removing the cellular components by apheresis. It contains clotting factors, proteins, and enzymes, and is used when these components are deficient or lost. It is hypothesised that in OP insecticide poisoning BuChE from FFP will sequester the poison present in the blood and remove it from circulation (Vučinić et al., 2013). However, the results of limited studies are controversial and there is no general agreement that it can be recommended for routine use for the treatment of exposure to OP compounds.

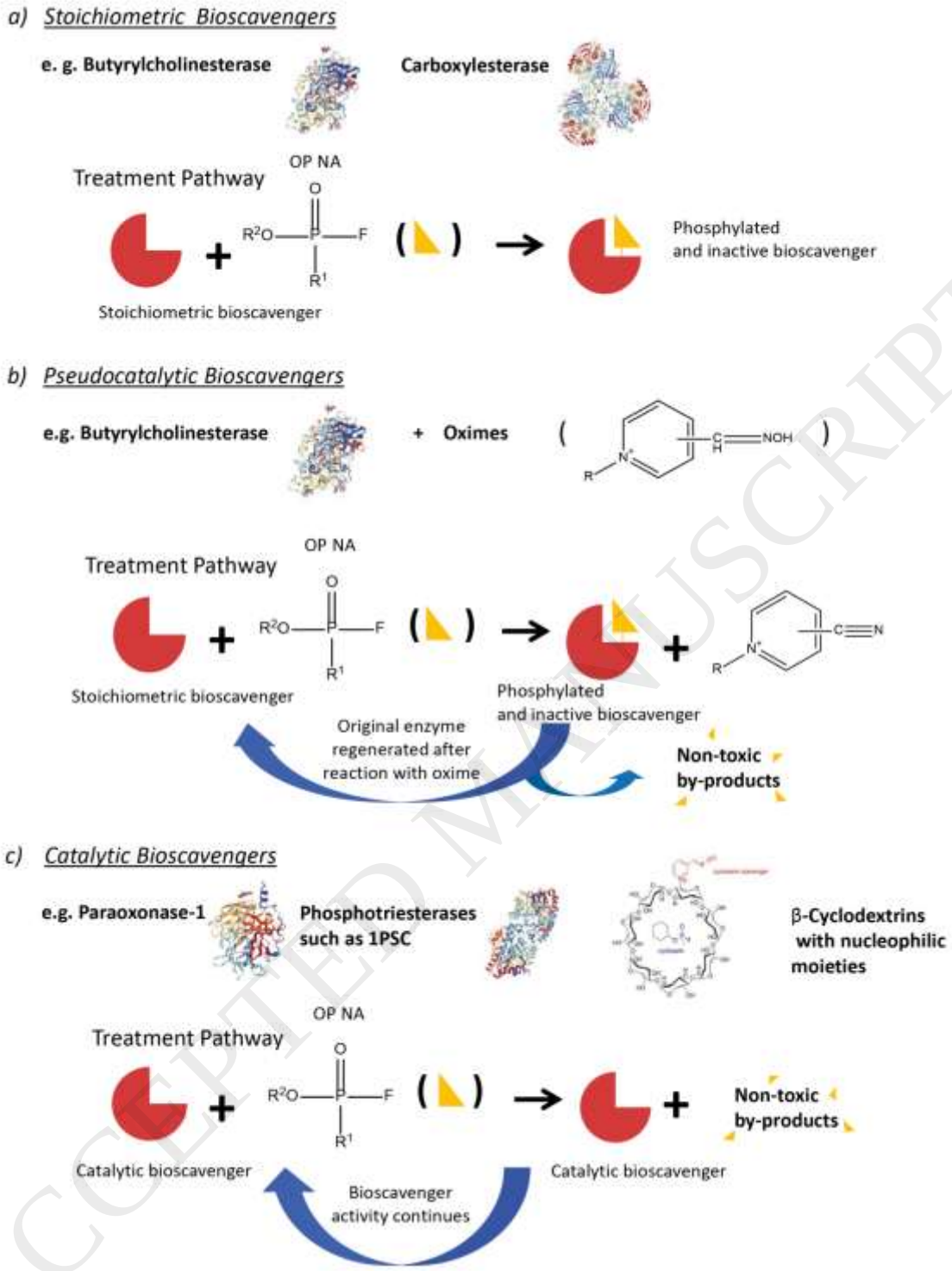

Figure 2. Classes of bioscavengers: (*a*) stoichiometric bioscavengers react with with NAs to form phosphylated adducts with loss of fluoride (G agents) or the *N*,*N*-dialkylethylaminothiolate (V agents) leaving group; (*b*) pseudocatalytic bioscavengers form similar adducts with NAs, but the addition of oximes allows the enzyme to regenerate and the NA to be converted into a non-toxic product; and (*c*) catalytic bioscavengers react with NAs,

release them as non-toxic products and regenerate the original enzyme, which can continue to function as a bioscavenger. The protein structures depicted were from the Protein Data Bank, and their indentifiers, in parentheses, are: butyrylcholinesterase (1P0I) (Nicolet et al., 2003), carboxylesterase (2HRQ) (Fleming et al., 2007), paraoxonase-1 (3SRE) (Ben-David et al., 2012), and phosphotriesterase (1PSC) (Benning et al., 1995).

3.4.2. Polysialylation of recombinant human BuChE (rHuBuChE) for long-acting NA bioscavengers

Chemical polysialylation of rHuBuChE has been used to produce bioscavengers that are stable in the bloodstream (Ilyushin et al., 2013). The CHO-based expression system for rHuBuChE resulted in a significant increase in the amount of functional bioscavenger that was stable in the blood, with better pharmacokinetic properties, and protection against 4.2 × LD_{50} of *O*-isobutyl *S*-2-(diethylamino)ethyl methylphosphonothiolate (VR).

4. Methods for decontamination of nerve agents

Decontamination of CWAs is generally based on three methods: (i) mechanical, (ii) physical, and (iii) chemical (Mondloch et al., 2015; Rosseinsky et al., 2015; Singh et al., 2010). It was described in a separate report by a member of the SAB (Martínez-Álvarez, 2014) and is covered in several reviews that should also be consulted (Jang et al., 2015; Yang et al., 1992). A decontaminant should be appropriate for the nature of the surface being decontaminated, for example bare skin, covered skin, or an inanimate object.

4.1. Oxidiser gels

To detoxify a NA, a formulation with a gelling agent (e.g. silica, alumina or aluminosilicate clays) and oxidising agent (aqueous sodium hypochlorite) can be prepared at the site of decontamination, and applied to the contaminated area (Farahipour et al., 2011). This approach is suitable for field implementation.

4.2. Bacterial phosphotriesterase

Phosphotriesterase (PTE) is an enzyme isolated from the bacterium *Pseudomonas diminuta* (Benning et al., 1995). Modified by biotechnological processes, with the redesign of the active site, engineered PTE enzymes are useful for detoxifying NAs *in vivo* (Blum et al., 2008; Briseño-Roa et al., 2006, 2011a, 2011b; Timperley et al., 2006; Worek et al., 2016).

4.3. Nanostructured solids and heterogeneous catalysts

Administration of reactive sorbent materials as oxidation promoters or photocatalysts that are activated by sunlight may be considered a new strategy for individual protection and decontamination in cases of exposure to CWAs (Wagner, 2010). Oxides of Zn, Ti, Fe, Mn, Mg, Al, Zr or Cu have a very high surface area and defective crystalline edges - corners and sites that are more reactive than the bulk material. These can be used to decompose NAs into non-toxic by-products. Nanomaterials, in particular ZnO-TiO_2 nanofibres obtained by electrospinning, are suitable for incorporation into textiles and clothes. Catalytically-active sites on the surface of zinc titanate fibres enable the slow hydrolysis of some NAs.

4.4. Nanosized metal oxides as CWA decontaminants

Having a high surface area, potent adsorbent properties and reactivity towards many CWAs, nanosized particles of MgO, Al_2O_3 and CaO are considered to be promising sorbent materials for removing NAs from contaminated surfaces and degrading them, leading to the formation of non-toxic products (Wagner et al., 2010). More recently, nanostructured clays and oxides for catalytic decontamination of CWAs have been reported (OPCW, 2017b).

4.5. Nanomaterials as active components in barrier creams

Identification of nanomaterials that can be used as reactive components of an active destructive material to treat a chemically-contaminated area is important (Braue et al., 2005). Topical skin protectants have been investigated since 1917, when different soaps and ointments were first used; after significant research since 2000, one has been approved by the US Food and Drug Administration (FDA), namely Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA) (Braue, 2005, 2011a-b; FDA, 2018; Timperley et al., 2018a). Excellent barrier properties are provided by this for protecting against soman and VX due to the presence of fine polytetrafluoroethylene (PTFE) solid dispersed in a

fluorinated polyether. Improvement of SERPACWA, by adjusting the amount of active nanomaterials, perfluorinated polyether oil, PTFE resin and other additives, increases the resistance against sulfur mustard (FDA, 2018).

5. Summary of response to the Director General's request

The responses to the Director-General's questions by the SAB are now provided:

(a) Identify best practices for preventing and treating the health effects that arise from acute, prolonged and repeated organophosphorus NA exposure

In the case of prolonged NA exposure, it is necessary to administer the adequate antidotal treatment consisting of a reactivator of NA-inhibited AChE, an anticholinergic drug to counteract the overstimulation of peripheral and central cholinergic muscarinic receptors, and an anticonvulsive drug to prevent centrally-mediated seizures and subsequent tonic-clonic convulsions, until the exposure to NA ceases. This treatment must continue as long as NA-induced clinical and laboratory signs and symptoms are visible. The oxime drugs should be administered at a dose regimen that allows the clinical improvement and the normalisation of AChE activity or until no further improvement is achieved (Timperley et al., 2018a).

To regulate repeated administration of reactivators of NA-inhibited AChE, it is important to measure the activity of cholinesterases in the blood (erythrocyte AChE and plasma BuChE) including a test of reactivation to evaluate the reactivating efficacy of the chosen oxime. Anticholinergic drugs should be administered until the signs and symptoms of atropinisation appear. Atropinisation should be visible for a longer time (within days). The anticonvulsive drugs should be given until the signs and symptoms of disturbed neuromuscular transmission and centrally-mediated seizures are visible. To regulate the repeated administration of anticonvulsive drugs, it is important to monitor the function of the central and peripheral nervous system, including EEG examination and muscle electromyography. Antidotal treatment should be supported by symptomatic treatment, including oxygenation, assisted ventilation, and the prevention of acidosis and infection, according to the severity of poisoning.

In the case of repeated NA exposure, each exposure must be treated the same way as the first exposure using adequate antidotes and supportive symptomatic drugs. It is necessary to note

that humans can be more sensitive to the acute toxicity of NAs in the case of repeated exposure because of the lower activity of AChE in the peripheral nervous system and CNS due to previous NA exposures (although changes of the activity of blood ChEs should not be very pronounced, monitoring of their activity is necessary). The prognosis of repeated exposure to NA is more severe and the antidotal and supportive treatment must be as intensive as possible.

(b) Identify any emerging medical countermeasures, intended for use at the point of exposure that can reduce or eliminate longer term health effects arising from acute, prolonged and repeated organophosphorus NA exposure.

The crucial approach - how to reduce or eliminate longer term health effects arising from acute, prolonged and repeated NA exposure - is to treat correctly the acute phase of poisoning (acute cholinergic crisis). Only rapidly administered adequate antidotal treatment consisting of a reactivator of NA-inhibited AChE (preferably the oxime HI-6 or obidoxime), an anticholinergic drug (preferably atropine), and an anticonvulsive drug (preferably a benzodiazepine), can stop the overstimulation of peripheral and central cholinergic receptors and subsequent clinical signs and symptoms.

Delayed and prolonged effects of NAs are mostly caused by damage to the CNS (frontal cortex, piriform cortex, hippocampus, and amygdala) through centrally-mediated seizures (due to prolonged overstimulation of central cholinergic muscarinic receptors and subsequent activation of glutamatergic receptors). To stop these seizures, it is necessary to prevent prolonged stimulation of muscarinic receptors by a centrally-acting anticholinergic drug (preferably scopolamine or benactyzine) and an anticonvulsive drug (preferably selected from diazepam, alprazolam, or midazolam during the initial seizures; with addition of other drugs such as ketamine during refractory status epilepticus that can only be properly treated in hospital). The antidotes must be administered as soon as possible to prevent delayed and prolonged health effects of NAs. If adequate medical countermeasures are insufficiently effective or are not realised sufficiently rapidly after the onset of NA poisoning, longer term health effects (especially neurological and including symptoms such as increased excitability and a deficit of cognitive function) emerge. In that case, the treatment is insufficient to eliminate such damage. However symptomatic and supportive treatment should be recommended in this situation.

The development of modern drugs for neuropathies is a need that must be taken into account by those researching treatments for OP-poisoning. Due to the potential dangers of intermediate syndrome following such poisoning, physicians should be aware of the occurrence of delayed neurotoxic effects, and should perform neuromuscular studies to rule out other causes and predict the severity of OP intoxication.

(c) The role of prophylactic antidotes against NAs in the prevention of longer term health effects arising from acute, prolonged and repeated exposure to organophosphorus NA compounds.

Prophylactic antidotes against NAs have been developed and introduced into military service to increase the resistance of the body against the acute toxicity of NAs and also to increase the efficacy of post-exposure antidotal treatment of NA poisoning. Prophylactic antidotes to NAs should be administered in response to the threat of exposure to NAs. Generally, the combination of the administration of prophylactic antidotes (pretreatment) and post-exposure adequate antidote treatment increases the probability of avoiding the delayed and prolonged effects of NAs resulting from CNS damage caused by centrally-mediated seizures (via protracted overstimulation of central cholinergic muscarinic receptors and the subsequent activation of glutamatergic receptors in the CNS).

Pyridostigmine bromide is a commonly advocated prophylactic antidote against NA poisoning (Timperley et al., 2018a). Unfortunately, it has several drawbacks. Its dosage is limited due to the risk of adverse effects and it cannot penetrate the blood-brain barrier. Thus, pyridostigmine can only protect peripheral AChE against irreversible inhibition by NAs. Therefore, a combined oral prophylaxis called PANPAL was developed, in the Czech Republic (Bajgar, 2009; Kassa, 2006). Clinical approval from the FDA and European Medicines Agency (EMA) would be necessary prior a general recommendation. PANPAL consists of a reversible AChE inhibitor (pyridostigmine) to protect peripheral AChE from irreversible inhibition by NAs and two centrally-acting anticholinergic drugs (benactyzine and trihexyphenidyl; chemical structures provided in Timperley et al., 2018a) to increase slightly the dose of pyridostigmine bromide and to antagonise the overstimulation of central cholinergic muscarinic receptors. This combination introduced into the Czech Army shows higher efficacy than pyridostigmine alone to avoid or at least diminish the acute toxicity and to prevent delayed and long-lasting health effects from acute, prolonged and repeated exposure to NAs (Bajgar, 2009; Kassa, 2006).

Another approach to increase the resistance of humans to NAs and the efficacy of post-exposure antidotal treatment of poisoning is to administer reactivators of NA-inhibited AChE in advance (Timperley et al., 2018a). In the Czech Republic, a special prophylactic antidote called TRANSANT (involving the oxime HI-6) was developed and introduced into service in the Czech Army (Bajgar, 2009). Clinical approval by the FDA and EMA would be necessary prior a general recommendation. This makes it possible to administer percutaneously the oxime HI-6 before exposure to NAs. The presence of HI-6 in the bloodstream enables the immediate reactivation of NA-inhibited AChE. The combination of both prophylactic antidotal means (PANPAL and TRANSANT) represents an effective prevention that is able to increase markedly the resistance of humans and prevent the centrally-mediated seizures, as well as subsequent delayed and prolonged health effects from acute, prolonged and repeated exposure to NAs.

A recent alternative approach to the development of prophylaxis in the case of threat of exposure to NAs is the administration of stoichiometric modified BuChE or catalytic bioscavengers (modified paraoxonase or phosphotriesterase) able to bind or hydrolyse NAs before they reach the target of their acute toxicity (AChE in the peripheral and central nervous system). This type of prophylaxis is valuable, but until now has not been prepared for clinical use. However, it represents a promising approach to preventing the longer-term health effects arising from acute, prolonged and repeated NA exposure.

6. Concluding remarks

This paper concludes the advice on assistance and protection given by the SAB on organophosphorus nerve agents to the Director-General and States Parties of the Convention in June 2015 (OPCW, 2015a). The findings of the SAB were presented to the delegations of States Parties on 8 July 2015 by Dr Slavica Vučinić (OPCW, 2015b) in a lecture held under the OPCWs Science for Diplomats initiative. The advice served as the foundation for the organisation of an international workshop on “Chemical Warfare Agents: Toxicity, Emergency Response and Medical Countermeasures” held in Paris, France, from 26 to 27 September 2016, that was realised by the OPCW in cooperation with the French Secrétariat Général de la Défense et de la Sécurité Nationale (OPCW, 2016c, 2016d).

Conflicts of interest

There are no conflicts of interest.

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Graphical abstract

Highlights

- Work of the Organisation of the Prohibition of Chemical Weapons (OPCW) is outlined
- Advice on assistance and protection from OPCW Scientific Advisory Board is provided
- Advice addresses medical care and treatment of longer term injuries from nerve agents
- Scientific literature on the topics is reviewed and over 130 references included
- This advice will better inform toxicologists, medics and emergency responders